Use of Recombinant Activated Factor VII to Treat the Acquired Coagulopathy of Trauma

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Recombinant activated factor VII (rFVIIa) is a drug commonly utilized in the treatment of patients with hemophilia and inhibitors. However, its use in previously normal patients with an acquired coagulopathy after trauma and surgery is increasing. Multiple trauma case reports and several case series are available, lending support for the efficacy of the drug in reversing the coagulopathy of trauma. Data from six large animal studies evaluating the efficacy in trauma models are available for evaluation. A single prospective randomized study in elective surgery has recently been published, documenting reduced blood loss and decreased transfusion after a single preoperative dose. This review describes those studies and reiterates the need for well-designed prospective, randomized human trauma studies.

Key Words: **Hypothermia, Coagulopathy, rFVIIa, Hemorrhage, Review.**

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Recombinant activated factor VII (rFVIIa) is a Food and Drug Administration (FDA)–licensed drug for the treatment of patients with hemophilia and inhibitors.[1–4] Use of rFVIIa in trauma has largely been for patients with profound coagulopathies after large-volume resuscitation, massive transfusion, and damage control procedures.[5–10] In the best of hands, trauma patients in this category have up to 50% mortality, and early death is almost entirely from uncontrolled hemorrhage.[11–14] New methods of hemorrhage control may serve to ameliorate some of these complications.[15] Combining new hemostatic approaches with conventional damage control methods is a potentially beneficial area of clinical research.

Animal studies have evaluated rFVIIa's effect on blood loss, blood pressure, survival, changes in laboratory values, and safety in models of acquired coagulopathy and/or severe liver or aortic injury.[16–21] A growing body of literature documents its apparently successful use in surgical and trauma patients. A recent prospective randomized study of patients undergoing elective radical prostrate resection documented decreased blood loss and transfusion requirements without increased thrombotic complications.[22] This review summarizes the preclinical trauma data and the rapidly expanding use of rFVIIa in previously normal patients after injury.

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Epidemiology

Uncontrolled bleeding is a major cause of death in civilian trauma victims.[23–25] Patients with isolated systolic hypotension (< 90 mm Hg) have up to 54% mortality,[26] and 50% require an urgent operation to control hemorrhage.[27] Sixty-five percent of deaths occur after admission to the hospital, and exsanguination is responsible for between 15% and 40% of hospital deaths among trauma patients.[23,24] Those patients acutely receiving more than 20 units of packed red blood cells have mortality of 50%.[11] Likewise, uncontrolled hypothermia secondary to hemorrhagic shock is an independent risk factor for mortality,[28] and hypothermia has been shown to be the most predictive element of the systemic inflammatory response syndrome criteria for developing multiple organ dysfunction syndrome.[29] Hypothermia is frequently found in patients after significant injury requiring massive resuscitation and serves to perpetuate coagulopathic bleeding. Unfortunately, rewarming these patients is time-consuming.[28] Acidosis both results from and contributes to coagulopathy and is difficult to reverse while patients are still bleeding.[30] Dilution of clotting factors occurs with massive transfusion, further compounding the acquired coagulopathy. The coagulopathy of severe trauma is multifactorial, with laboratory values resembling those found in sepsis-induced disseminated intravascular coagulation (DIC).[31] Whereas the treatment of sepsis-induced DIC is focused on elimination of the source of sepsis, the treatment of trauma-induced DIC is focused primarily on hemorrhage control, rewarming,[32,33] factor replacement,[34] and resuscitation.[35] These efforts usually take hours to accomplish and are often fruitless without definitive control of the ongoing bleeding.

The combination of hypothermia, coagulopathy, and acidosis is a self-perpetuating vicious cycle that is rapidly fatal unless interrupted.[12] The potential benefit of breaking the vicious cycle with an injectable drug that rapidly treats the acquired coagulopathy of trauma is significant.

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Mechanism of Action

The drug that currently holds the most promise for reversing the acquired coagulopathy associated with trauma and massive hemorrhage is rFVIIa. When bound to exposed tissue factor (TF), normally expressed FVIIa activates the extrinsic clotting system at the site of injury without causing systemic hypercoagulability. rFVIIa is an attractive candidate as therapy for coagulopathy because it bypasses much of the intrinsic coagulation system, is active only in the presence of exposed TF, and has a rapid onset and a short half-life.[3] TF is not normally expressed in the intact vascular space but exists in high concentrations in the media and is exposed upon vessel injury. TF can be expressed on the surface of activated monocytes after sepsis; however, the significance of this is unclear, as TF activity (the biologically functional form of the molecule) has not been measured.[36] An alternative hypothesis is that rFVIIa acts by binding to activated platelets and activating FXa on the platelet surface, independent of the usual TF cofactor.[37]

Preclinical Data

Six large animal studies at four different laboratories have been completed, evaluating the optimal dose, efficacy, and how best to use rFVIIa. These studies broadly fall into two categories: those that evaluate the drug as a single therapeutic agent and those that evaluate the drug as an adjunct to surgical therapy.

Utilizing rFVIIa as a Single Therapeutic Agent

Lynn et al. have described an experiment in which a pig liver-injury model was utilized to evaluate the hemostatic efficacy of rFVIIa as the sole agent for hemostasis.[18] This model mimics a prehospital situation in which a patient suffers a truncal injury (noncompressible by the medic) and rFVIIa is utilized as the sole hemostatic agent. rFVIIa (180 μg/kg) was given 30 seconds after injury, and no other hemostatic interventions were applied to the liver. The animals were normothermic, not resuscitated, and followed for 60 minutes after injury. The blood loss was numerically lower in the study group (27.6 $\pm$ 2.1 mL/kg versus 33.3 $\pm$ 3.4 mL/kg; $p = 0.2$), but the results were not significantly different. Similarly, mortality in the study group was 0 of 6, but in the placebo group it was 3 of 7 (43%; $p = 0.08$). Significantly, 5 minutes after injury and for the remainder of the study period, the rFVIIa group sustained a higher mean arterial blood pressure (MAP) than the placebo group ($p < 0.05$). As in all animal studies, the PT was shorter than in the placebo group ($p < 0.05$). In this grade IV liver-injury model, rFVIIa, when utilized as a single agent for hemostasis, preserved blood pressure and shortened PT but by itself did not significantly decrease blood loss or improve survival.

Subsequently, Jeroukhimov et al. published a study in which two different doses of rFVIIa (180 μg/kg and 720 μg/kg) were evaluated in the same prehospital liver-injury model.[19] The higher-dose group demonstrated improved survival and decreased blood loss ($p < 0.05$) 60 minutes after injury. No evidence of microthrombi was seen in the kidney, small intestine, lung, heart, or brain.

Schreiber et al. recently completed a liver-injury study utilizing rFVIIa as the sole agent for hemostasis.[20] They utilized rFVIIa (150 μg/kg) in a grade V liver-injury model, injecting the drug 30 seconds after injury. The pigs were normothermic, fluid resuscitated 15 minutes after injury, and followed for 120 minutes. The blood loss over the first 15 minutes was similar (822 mL in the rFVIIa group and 768 mL in the placebo group). Likewise, at the completion of the study, the amount of blood in the peritoneal cavity was 397 mL in the rFVIIa group and 437 mL in the placebo group. As expected with similar blood losses, the MAP did not differ between groups. Prothrombin times 1 minute after injury were shorter in the rFVIIa group than in the placebo group ($p < 0.05$). Histologic analysis of lung tissue revealed no evidence of microthrombi in either group. In this normothermic grade V liver-injury model with early drug delivery and rapid resuscitation, utilizing rFVIIa as sole therapy did not alter blood loss or blood pressure.

Utilizing rFVIIa in Conjunction with other Standard Hemostatic Therapies

Martinowitz and colleagues published a report on utilizing rFVIIa as adjunctive therapy in a hypothermic, coagulopathic grade V liver-injury model.[16] All animals underwent a 60% isovolemic exchange transfusion with 6% hydroxyethyl starch (MW 200,000) and were cooled to 33°C core temperature. The swine sustained a grade V liver injury and, 30 seconds later, received either 180 μg/kg rFVIIa or saline control. The animals were packed with gauze laparotomy pads after injury and resuscitated with lactated Ringer's solution. Post-treatment blood loss, MAP, resuscitation volume, and clotting studies were monitored for 1 hour. Blood loss was less ($p < 0.05$) in treated animals (527 $\pm$ 323 mL) than in controls (976 $\pm$ 573 mL). One-hour survival in both groups was 100%. Compared with the control group, rFVIIa increased the circulating levels of FVIIa and shortened the prothrombin time 5 minutes after injection ($p < 0.05$). The study group did not have visible large clots in the hepatic veins or the inferior vena cava or microscopic thrombi in lung, kidney, or small intestine. The laboratory tests that evaluated systemic activation of the clotting cascade, thrombin activating time, and platelet adhesion, as well as the thromboelastogram, were not different between the two groups. Histologic evaluation of pulmonary tissue revealed no evidence of microthrombi. In this hypothermic, diluted, hypotensive trauma model, there was no identifiable laboratory evidence of systemic activation of the clotting cascade by rFVIIa. When utilized in conjunction with liver packing, rFVIIa decreased blood loss without identifiable adverse effects.

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Schreiber et al. recently published another study in hypothermic (33°C), dilutionally coagulopathic pigs with grade V liver injuries treated with rFVIIa and gauze packing.[17] These animals were treated with resuscitation and gauze packing instituted 30 seconds after injury, followed by intravenous injection of rFVIIa. This study evaluated two different doses of rFVIIa: 180 μg/kg and 720 μg/kg. There was no difference in blood loss between the two treated groups (1,086 ± 227 mL and 1085 ± 289 mL), but there was a decrease in blood loss between the rFVIIa-treated and control group (2,187 ± 577 mL; $p < 0.05$). There was no evidence of gross clot or premortum microthrombi formation.

Sondeen et al. have documented that injecting rFVIIa before an aortic injury in swine did not decrease the amount of blood loss or the depth of hypotension. However, it did result in a stronger clot that was more resistant to rebleeding in comparison with controls ($p < 0.05$). This allowed resuscitation back to a normal preinjury level, prevented rebleeding, and decreased the metabolic consequence of prolonged hypotensive resuscitation techniques.[21]

In summary, six animal studies have evaluated the role of rFVIIa as a hemostatic agent in previously normal animals with severe injuries. These studies evaluated different combinations of liver and aortic injuries, temperature, resuscitation strategies, and dose regimens. Three studies were of warm, coagulation-intact animals in which the rFVIIa was the only hemostatic agent utilized. One of these experiments demonstrated preserved blood pressure,[18] whereas another showed decreased blood loss and improved survival.[19] The third study revealed no difference in either blood pressure or blood loss.[20] Two other studies were completed in cold, dilutionally coagulopathic animals with grade V liver injuries.[16,17] Both studies utilized rFVIIa as an adjunct to gauze packing, much as it has been used in many off-label trauma cases. The laboratory changes of coagulopathy were corrected within minutes of administration. These two animal studies both demonstrated a 46% decrease in blood loss in the rFVIIa-treated animals.[16,17] Last, the recently completed aortic-injury study documented an increased rebleeding pressure, physiologically indicating stronger clot formation.[21] Significantly, despite specific searches for evidence of microthrombi, none of the animals in any of these various studies demonstrated any evidence of thrombotic complications.

Human Data

Use of rFVIIa as an adjunct to standard hemostatic maneuvers when treating trauma patients in a damage-control mode is no longer unusual. Many trauma centers routinely utilize the drug as an adjunct in their efforts to decrease coagulopathic bleeding in these critically ill patients. Our institution and others have instituted an rFVIIa clinical practice guideline to manage this new therapy.

Kenet et al. described the first use of rFVIIa in a trauma patient in 1999.[5] The patient was a young soldier with a gun shot wound to the abdomen, injuring, among other structures, the inferior vena cava. rFVIIa was given in a desperate attempt to control the massive coagulopathic bleeding. The intervention was successful and the patient ultimately survived. In 2002 O'Neil and associates described the first use of rFVIIa for trauma in the United States.[7] Their patient suffered numerous stab wounds, and despite heroic efforts, consisting of three operative explorations and two angiographic embolizations, the patient continued to bleed 45 hours after injury. After 105 units of packed red blood cells (PRBCs) they administered 90 μg/kg of rFVIIa. The patient stopped bleeding immediately but ultimately died of sepsis 5 weeks after injury. An autopsy revealed no evidence of thrombi.

Martinowitz et al. in 2001 published a report of their first seven trauma patients who received rFVIIa.[6] The patients had blunt and penetrating trauma and received 25–49 units of PRBCs before receiving rFVIIa. The dose in this group of patients ranged from 120 to 212 μg/kg. Three of the seven patients died, but the surgeons describe how the coagulopathic bleeding ceased, thus allowing the surgical bleeding to become obvious and therefore be easily controlled by conventional means. The group in Israel has since treated more than 40 patients with rFVIIa, with similar encouraging results (personal communication, Dr. Uri Martinowitz). I have utilized the drug with results similar to those described by Martinowitz.

In a landmark article Freiderich et al. reported their successful experience in the first prospective, randomized, double-blinded, placebo-controlled trial, describing use of rFVIIa in radical prostate surgical patients.[22] A placebo treatment arm was compared with two treatment groups receiving either 20 or 40 μg/kg of rFVIIa. Blood loss was decreased in the rFVIIa groups ($p < 0.01$), and transfusions were eliminated in the higher-dose group. Operative time decreased in the rFVIIa group (120 versus 180 minutes; $p < 0.05$). No deleterious safety issues were identified, and the group of older, procoagulant males receiving rFVIIa did not manifest complications associated with hypercoagulopathy.

Although the final results have not yet been published, Boffard et al. recently presented the results of a multicenter (32 centers in 8 countries) prospective, randomized, placebo-controlled, double-blind trial of the efficacy and safety of rFVIIa as adjunctive therapy for hemostasis in trauma patients.[38] Two hundred seventy-seven patients, equally divided between blunt and penetrating injuries, were enrolled. Patients received the first dose of rFVIIa following the 8th unit of PRBCs, with additional doses 1 and 3 hours later (200 + 100 + 100 μg/kg). Standard treatment was then utilized at each site. The primary endpoint was transfusion requirements or the number of PRBC units within 48 hours of the first dose. In blunt trauma patients, PRBC transfusions were reduced by 2.6 units ($p = 0.02$), and the need for massive transfusion (> 20 PRBCs) was reduced (14% versus 33% of patients; $p = 0.03$). For those patients with penetrating trauma, there was a trend toward a reduction of PRBCs (1.0 RBC units, $p = 0.10$) and massive transfusion (7% versus

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19%; $p = 0.08$). No safety issues, including thromboembolic events, were identified in the study. This important work clearly shows that rFVIIa is safe in severely injured trauma patients and resulted in decreased transfusions in blunt trauma patients. Patients with penetrating injuries also had decreased transfusions, but the results were not statistically significant. This phase II trial will help to pave the way for a pivotal phase III effort for a multi-institutional study of massive hemorrhage. This phase II trial also highlighted the need for consistent treatment guidelines, including massive transfusions.

An increasing number of published case reports document the use of rFVIIa in patients with acquired coagulopathy from a variety of conditions such as trauma,[5–10] head injury,[39,40] cirrhosis,[41] bone marrow transplant,[42] gastrointestinal bleeding,[43] heart valve replacement,[44] sepsis induced diffuse intravascular coagulation,[45,46] liver transplantation,[47] necrotizing pancreatitis,[48] pulmonary alveolar hemorrhage,[49] and coronary artery bypass.[50] Patients with cirrhosis and chronically elevated PT have been treated with rFVIIa and demonstrated normal coagulation parameters within 1 minute of injection.[40] Along the same lines, it has been used to rapidly reverse the effect of coumadin anticoagulation in healthy volunteers, for up to 24 hours.[51] These multiple case reports document varying levels of effectiveness but no adverse outcomes directly attributable to the drug. In the 14 years rFVIIa has been clinically used, only a few cases of myocardial infarction and stroke have occurred, supporting the claim that a very limited number of thromboembolic events have resulted despite widespread use.[3,52–54]

Patients who initially survive massive hemorrhage and sepsis may ultimately succumb to multiple organ failure.[55] Initially Hardaway and more recently Gando described the possible relationship between diffuse microthrombi and organ failure.[31,56–58] It is theoretically possible that modulation of the coagulation cascade with rFVIIa to improve local hemostasis could result in an increased incidence of late multiple organ failure due to increased systemic microthrombi formation and fibrin deposition. However, none of the uncontrolled case reports lend credence to this theory. None of the controlled animal trauma studies that focused on the hemorrhage-control aspects of rFVIIa have documented any evidence of increased thrombotic complications, despite meticulous histologic and laboratory evaluation of this specific question. An ongoing prospective, randomized, blinded human trauma trial outside the United States will lend insight to the critical questions of safety and efficacy.[38] The concern that systemic delivery of rFVIIa will cause increased diffuse microthrombi has not been supported by data from controlled animal studies. Likewise, the growing body of data from controlled and uncontrolled human studies in nonhemophilic patients has not indicated significant thrombotic complications.

Future Use

As understanding increases about how to optimally modulate the coagulation and inflammatory response to injury, an intriguing possibility is to upregulate coagulation early in exsanguinating patients and then later downregulate the system with *inactivated* rFVIIa.[59] Preclinical data suggest that this concept may be possible.

The potential also exists for successful use of rFVIIa in remote surgical locations where more traditional therapy for traumatic coagulopathy (platelets, fresh-frozen plasma, cryoprecipitate, and rewarming capability) are unavailable, such as in rural areas and deployed small military units. In these situations an injectable adjunct for hemorrhage control may prove very valuable, especially with the onset of hypothermia and coagulopathy. A clinical practice guideline has been established for this situation. A logical extension of the injectable adjunctive hemostasis approach is for prehospital personnel to utilize the drug as a single agent to bridge the gap between injury and hospital admission. In this setting the drug would be used as an injectable hemostatic agent for noncompressible hemorrhage. The studies by the Miami group[18,19] may support this approach, and further preclinical study is required in this arena. A focused research effort is required to decrease deaths from cavitary hemorrhage that is not amenable to manual compression by prehospital personnel. This effort is ongoing within the Department of Defense.

SUMMARY

In conclusion, over the last 4 years, a growing series of preclinical and human data have indicated the potential usefulness of this drug in patients with acquired coagulopathies from both blunt and penetrating injuries. Six large animal trauma studies have been performed, with no apparent evidence of systemic microthrombi. Five of the six animal studies showed decreased blood loss, improved survival, or stronger clot formation. Martinowitz and colleagues in Israel have continued to accumulate significant experience with the drug, and a prospective trauma trial is under way outside the United States. Multiple trauma centers around the United States are routinely utilizing rFVIIa for coagulopathic trauma patients. One unit has recently administered the drug over 50 times to coagulopathic trauma patients.[10] A recent prospective elective-surgery study documented decreased blood loss and transfusions, without increased thrombotic complications.[22] Despite these encouraging results, questions about the optimal dosing regimen and safety continue to linger. Pharmacoeconomic studies are urgently required, because the drug is expensive.[60] Newer, more potent formulations of the drug are under development.[61,62] With increased focus on hemostasis research, improved understanding of the coagulation cascade is emerging.[63] These efforts have resulted in credible discussions about utilizing the drug as a temporizing hemostatic agent in prehospital scenarios. A series of prospective, randomized, blinded human trauma trials in the United States are

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urgently required to answer the provocative questions raised by the animal and human studies.

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